Introduction to Philosophy of Systems Biology

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Chapter 1

Introduction to Philosophy of Systems Biology

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The intention with this volume is to provide a format for scholars to express their personal viewpoints and tell their story in response to the same set of questions (see Preface). Unlike many edited volumes, this book is therefore not divided into thematic sections. The aim of this introduction is to summarize core common themes among the contributor's chapters so as to guide readers interested in specific topics. Given the richness of the contributions that touch upon many diverse topics in response to the posed questions, I have not summarized each contribution separately. Rather, I focus on core questions and highlight where more information on common themes and novel insights can be found. I also hope that the introduction will provide some background for scientists, philosophers as well as other readers interested in discussing the philosophical implications of systems biology.

1. What is systems biology?

Broadly understood, systems biology aims to capture the dynamic complexity of living systems through the combination of mathematical, computational and experimental strategies (Kitano 2001). One overarching research question is how biological function emerges from the interactions of processes whose dynamics are nonlinear and constrained by the organization of the system as a whole (cf. Wolkenhauer, Chapter 24). Research in systems biology is driven by complex problems requiring interdisciplinary solutions, but there are different views on the most significant methods, values and aims of systems biology. Some scholars emphasize computational integration of big data from multiple sources as a characteristic feature of systems biology (Aderem 2005), whereas others stress that systems biology is a merger of systems theory with biology (Wolkenhauer and Mesarović 2005). Differences in theoretical and methodological standpoints are sometimes characterized by the differences between pragmatic and systems-theoretical systems biology: the former sees systems biology as a straightforward extension of genomics and molecular biology and the latter highlights the need for a formal systems theory of living systems (O'Malley and Dupré, 2005, for further reflections see Boogerd et al. 2007). In both cases, however, researchers must navigate in what Nersessian (Chapter 20) calls an *adaptive problem space* where knowledge and methods are continuously reconfigured and combined into new hybrid methods, concepts, and models. The combination of theoretical reflection and technologically mediated methodological innovations make systems biology particularly intriguing from a philosophical perspective.

It is debatable whether systems biology brings something radically new to the life sciences. Systems biology has been described in terms as different as a new 'holistic paradigm' or 'revolution' in biology to being merely a 'buzzword' used for funding purposes (Kastenhofer 2013b). It is difficult to point to radical historical shifts or 'revolutions', but systems biology develops in a unique historical and technological context offering new and exciting opportunities for data production, modeling and also for conceptual development. Systems biology combines traditional biological research strategies with methodological and theoretical frameworks from various disciplines including physics, engineering, computer science, and mathematics. As Boogerd (Chapter 4) notes, systems biology is perhaps unprecedented in the extent to which various disciplines are combined, and is already a diverse and rapidly expanding approach. Moreover, the view that systems biology is old and new at the same time (e.g., Westerhoff and Hofmeyr 2005) is echoed by several contributions in this volume. Whereas the label of systems biology only recently gained currency, systems biology has many important precursors and many researchers have been doing systems biology research for several decades. To mention a few examples, Noble (Chapter 21) developed the first viable mathematical model of the beating heart in the early 1960s, Davidson (Chapter 6) and Britten formulated a gene regulatory network (GRN) model in 1969, and Mesarović (Chapter 19) and Takahara developed a theoretical framework for multi-level hierarchical systems in the 1960s and 1970s. Similarly, several scholars have pushed for systems approaches to the dynamic control of biological processes for many years before the term systems biology was used in its modern context (e.g., Hofmeyr, Chapter 11; Hohmann, Chapter 12; Voit, Chapter 23). The development of systems biology is therefore a long process with different theoretical and methodological roots. I shall first give a brief overview of some early precursors of systems biology and then move to the development of systems biology in the modern context.

Mesarović coined the term systems biology as early as 1968 at the Third International Systems Symposium at Case Institute of Technology, Cleveland, Ohio (Mesarović 1968). Systems biology in this initial context concerned the launching of a biological research field based on Mathematical General Systems Theory, inspired by the aim in cybernetics to identify and formulate mathematical principles underpinning functional capacities such as feedback control. The potentials of this framework for conceptual advance in biology is still being explored (Mesarović, Chapter 19; Wolkenhauer, Chapter 24). Weiss and Bertalanffy are other precursors whose work is of continued relevance for theory development in contemporary systems biology (see Drack, Chapter 7; Mekios, Chapter 18). Similarly, Fagan (2012) highlights how many aspects in Waddinton's theoretical biology anticipate modern systems biology ideas, including the emphasis on global and dynamic epigenetic properties as a prerequisite for understanding development and heredity (see also Fagan, Chapter 8). Other branches of systems biology draw inspiration primarily from the development of Metabolic Control Analysis, Savageau's Biochemical Systems Theory, or Rosen's theoretical framework for metabolic repair-systems (for references see Hofmeyr, Chapter 11; Voit, Chapter 23). Noble (Chapter 21) traces the history of systems biology even further back to Claude Bernard, who introduced the principle of homeostasis in 1865. Moreover, Noble highlights how, already two centuries earlier (in 1665), the philosopher Benedict de Spinoza stressed the importance of system-level constraints on component parts. What is common to all of these is the acknowledgment of the profound complexity of living systems, requiring approaches that can understand biological function in the context of the system as a whole. Another shared view is that a formal theory of complex systems may be needed for this purpose.

Systems biology challenges the view, encountered by many modelers, that biological complexity is incompatible with the aims of formal mathematical analysis (see Voit, Chapter 23; Wolkenhauer, Chapter 24). As Voit observes, the view that biological systems are too complicated to be amenable to mathematical analysis has now been turned on its head; Biological systems may be too complex to understand without the use of math. Importantly, the upgraded role of mathematical and computational modeling in biology should also be understood in terms of a historical and technological context of systems biology that makes such tools a necessity. Ironically, perhaps, the culmination of the success of reductionist and gene-centric strategies in biology resulted in an increasing realization of the limitations of approaches investigating isolated molecular components or pathways (see e.g., Lazebnik 2010; Voit, Chapter 23; Wolkenhauer and Green 2013). One should avoid any oversimplified contrast between molecular biology and systems biology as the relation between these are complex and far from clear-cut (see e.g., Bechtel, Chapter 2; Fagan, Chapter 8; Gross, Chapter 10). But as new insights to biological complexity emerged with improvements for data-production, it became clear that traditional modeling tools in biology were insufficient both for handling the huge amount of data and for studying the *regulatory dynamics* of complex networks (Jaeger, Chapter 13; Hohmann, Chapter 12; Peter, Chapter 22). Systems biology, broadly speaking, involves a "quantitative turn" (Bentele and Eils 2005) where researchers complement studies of qualitative properties of specific molecules with a search for dynamic patterns in large networks based on quantitative data on biological interactions. It is important to note, however, that in addition to this "top-down" approach, other strategies in systems biology are better described as a bottom-up approach (Krohs and Callebaut 2007). The differences are not clear-cut but generally top-down approaches aim to "reverse engineer" regulatory patterns in large datasets from high-throughput technologies, whereas bottom-up or middle-out approaches draw on more detailed (but often less comprehensive) data from molecular biology sources (see also Nersessian, Chapter 20).

Kitano (Chapter 16) started using the term "systems biology" in this modern context in the late 1990s. This was the period leading to the completion of the Human Genome Project and the first big-data modeling projects (see also Kitano 2002a; 2002b). This modern notion of systems biology rapidly gained currency with institutional developments from 2000 and onwards, including the emergence of international conferences on systems biology (the first in Tokyo in 2000), departments of systems biology and journals dedicated to work in systems biology. The fast development of systems biology in the 21st Century shows that technology is not just a tool in science but can also give rise to new fields through the generation of unexpected results and exploration of a new set of research questions (Bertolaso, Chapter 3; Kastenhofer, Chapter 15; O'Malley and Soyer 2012). Moreover, systems biology provides new opportunities for data-intensive biomedical research strategies such as multi-scale models and simulations (Kolodkin, Chapter 17; Kohl and Noble 2009) with profound epistemic, social and ethical implications (Carusi, Chapter 5).

Methodological and theoretical discussions in, and about, systems biology bring new light on many classical philosophical topics. Examples are reductionism, scientific explanation, modeling, the relation between theory and experiment, interdisciplinary collaboration, and the role of mathematics, engineering and physics in biology. They also have implications for more fundamental ontological debates about what life is and how to describe living systems. Moreover, new questions are raised such as the implications of network modeling and large-scale simulations. Contributions in this volume also comment on broader types of scientific methods and the culture of science. Below I shall further unpack some of the questions that are taken up in these debates and emphasize how systems biology brings new life to these discussions.

2. Topics in Philosophy of Systems Biology

Reductionism and emergence

As mentioned above, systems biology is often defined in opposition to reductionist methodologies. The dictum that *the whole is more than the sum of the parts* highlights the philosophical and scientific interest in so-called emergent properties, i.e. properties of the system that cannot be explained or deduced from the parts alone (Kolodkin, Chapter 17; Mekios, Chapter 18). The modern cliché has very old roots in philosophy going back to Aristotle, but systems biology brings new light to the question of how "more" is to be understood in this context. An important question from the outset has been what *kind* of emergence systems biology supports (Alberghina and Westerhoff 2005; Boogerd et al. 2005; 2007; Kolodkin, Chapter 17; Kolodkin et al. 2012;). These discussions consider ontological discussions about the nature of living systems but also epistemic issues about the appropriate methodology for investigating these.

Numerous contributors engage the issue of the extent to which systems biology breaks with reductionism and what it means to say that systems properties emerge (e.g., Bechtel, Chapter 2; Boogerd, Chapter 4; Gross, Chapter 10; Voit, Chapter 23; Wolkenhauer and Green 2013). The focus on gene regulatory networks, rather than static DNA sequences as "codes", is a crucial step towards a more nuanced view on the complexities of the relations between genotypes and phenotypes (Davidson, Chapter 6; Noble, Chapter 21; Peter, Chapter 22). Systems biology in this sense entails a different epistemology and ontology focused on the dynamic regulation of biological systems (Bertolaso, Chapter 3). Specifically, Jaeger (Chapter 13) calls for a *process ontology* that also requires new methodological approaches to reach its potential. Equally important is whether studying processes at the molecular level is sufficient for understanding macroscale properties, or whether a multi-level analysis is needed (Bertolaso 2011; Chapter 3; Mesarović and Sreenath 2006; Wolkenhauer, Chapter 24). Contributions in this volume provide different views on the question of whether a specific level or scale can be said to have causal priority. For instance, Davidson (Chapter 6) argues that research on regulation of developmental processes must begin with genomic regulatory information in which biological functions are “determinatively encoded”, whereas others express skepticism about the causal priority of gene regulatory networks (e.g. Noble, Chapter 21). Examples of multi-scale modeling in the context of research on cardiac simulations, developmental biology and cancer research are particularly illuminating for addressing this question (Bertolaso, Chapter 3; Bertolaso 2011; Noble, 2012; Wolkenhauer, Chapter 24).

Importantly, some contributors highlight how a non-reductive stance also entails an understanding of how living systems in some ways are *less than the sum of the parts*, because we need to account for how system-level constraints influence the behavior of the parts (Hofmeyr, Chapter 11; Noble, Chapter 21; Noble 2012; Wolkenhauer, Chapter 24). Hofmeyr (Chapter 11) clarifies how the activities of enzymes are constrained by the chemical environment and the cellular context, whereas Noble (Chapter 21) highlights the importance of cellular and tissue-scale constraints for pulse-generating oscillations responsible for heart rhythms. Such examples can illuminate philosophical discussions on the difficult concepts of downward causation and hierarchical control (Bertolaso, 2011; Bertolaso, Chapter 3, Mesarović, Chapter 19; Noble, Chapter 21). The discussion also has practical implications. Theoretical debates about whether cancer is a genetic disease caused by mutations or reflects a problem of tissue organization also concern questions about the most relevant methodology, e.g. whether the way forward in cancer research is to invest more in cancer genomics or to study tissues *in vitro* and *in silico* (Bertolaso, Chapter 3; Soto and Sonnenschein 1999; Wolkenhauer, Chapter 24). Thus, reasoning about biological systems in a certain way can have important practical and societal implications, and this is one reason why reflection on the underlying assumptions of scientific practice is relevant for philosophers and scientists alike.

Mathematical and computational modeling in systems biology

Mathematical and computational models are increasingly considered indispensable for understanding biological complexity, and for integrating and interpreting the vast amount of data from high-throughput technologies. Rather than analyzing the details of a specific molecular pathway, much research in systems biology is concerned with pattern detection in the architectures of networks representing interconnected regulatory interactions. Understanding the implications of the use of graph-theoretical tools for analysis of biological organization has become an important topic in philosophy of systems biology. Graph-theoretical analysis spans historically from analysis of random networks and regular lattices, to the recent discovery that many networks share a small-world and scale-free structure with important implications for their functions (see Bechtel, Chapter 2). The importance of global network analysis for biological research is a controversial issue, and an important question is whether systems biology can bridge the gap between the local and global approaches (Gross, 2013; Chapter 10). Bechtel highlights one candidate for a middle-way, namely the search for frequently occurring patterns of connections (see also Peter, Chapter 22).

One example that has already received much attention from philosophers of biology is Alon’s pioneering work on motif-analysis, i.e., overabundant subcircuits such as feedforward loops (Alon 2007; Bechtel, Chapter 2; Green 2013; 2014; Levy and Bechtel 2013). The search for generalizable patterns of network circuitry is also exhibited in research on developmental processes (Peter and Davidson 2015; Peter, Chapter 22), on biochemical reaction networks (Alves and Sorribas 2011; Tyson and Novác 2010), and on robustness in various biological systems (Green 2015b; Stelling et al. 2004). Although the quest to identify design principles realized in biological circuits goes back to the earlier systems-theoretical approaches mentioned above (see also Green and Wolkenhauer 2013; Mesarović, Chapter 19; Savageau 1985), the detection of motifs in regulatory networks received special attention because it was based on high-throughput data and because mathematical predictions were coupled to experimental investigations. The revival of the interest for general design or organizing principles has also given rise to discussions about the extent to which living systems, despite the complexity of intertwined processes, are constituted by individual functional units that exhibit modularity (cf. Green 2015a; Gross, Chapter 10; Isalan et al. 2008, Peter et al. 2012; Peter, Chapter 22). Moreover, the renewed interest in mathematical analysis of organizational features has led to discussions about the implications of abstraction from molecular details for the sake of identifying generalizable organizational features (Green and Wolkenhauer 2013; Levy and Bechtel 2013; Wolkenhauer, Chapter 24). The implications of such principles for philosophical accounts of explanation will be discussed separately in the section on design principles below.

Another important aspect of mathematical and computational modeling in systems biology concerns the integration and interpretation of data in large-scale simulations. Large-scale models and simulations have exciting potentials for medical applications (Carusi, Chapter 5), but also raise important epistemic questions about (i) the extent to which biological complexity can be meaningfully captured *in silico* (e.g., Gramelsberger, Chapter 9; Kolodkin, Chapter 17), (ii) how models from engineering, physics and mathematics are combined (e.g., Nersessian, Chapter 20), and (iii) the potential and need for developing a new mathematical framework or artificial language specifically suited for dealing with biological complexity (e.g., Gramelsberger, Chapter 9; Kitano, Chapter 16).

Kastenhofer (Chapter 15) ponders about what criteria should be fulfilled in order to speak of “whole-cell modeling” and what levels of performance of model prediction it is realistic to achieve. These are important open questions for current and future research. We are currently witnessing ambitious efforts to develop whole organ or whole ‘digital patient’ models encompassing biological complexity in an unprecedented way (Kohl and Noble 2009; Kolodkin et al. 2011). But it is an open question how far such developments will take biomedical research. Gramelsberger (Chapter 9) highlights how challenges for simulating complex processes in meteorology and other computational sciences are increasingly relevant as biology is starting to develop complex computational models. In comparison to established computational fields, she describes the current situation in biology as the “wild west” due to the variety of different approaches, making many models difficult to understand and reuse (see also Gross, Chapter 10). To understand the results of algorithmically constructed models, philosophers and biologists alike must increasingly make efforts to understand the mathematical techniques involved. Debates concern not only which models are most appropriate for specific purposes and how these should be combined, but also whether we are in need of a novel digital language to reason about biological functions. Kitano (Chapter 16) argues that our natural language is often an obstacle for biological research because it is metaphorical and context-sensitive, and thus imprecise. In his view, the best way to overcome the problem is to develop computational approaches and an exact and systematic artificial language (see also Kolodkin, Chapter 17). One such initiative is the Systems Biology Markup Language (SBML, 2011) whose purpose is to serve as a machine-readable *lingua franca* that enables communication and translation between software programs. However, it remains to be seen whether initiatives such as the SBML will lead to important breakthroughs, or whether they will “choke progress and academic freedom” (Voit, Chapter 23).

Large-scale modeling also brings up the issue of the relation between the size of datasets and the predictive power of models. Some contributors are optimistic that more comprehensive datasets and powerful computational simulations can overcome many limitations of current models (Kolodkin, Chapter 16) and even deal with Popper’s “black swan” problem (Davidson, Chapter 6). The “black swan” in this context is an unexpected finding in scientific inquiry, used by Popper (1959) to illustrate the logical asymmetry between verification and falsification of scientific hypotheses. Regardless of how many observations appeared to support the idea held by Europeans until the 17th Century that all swans are white, it only took one single observation of a black swan to falsify it. Whereas Popper’s theory sought to strengthen scientific methodology against the problem of induction, the consequence of the incompleteness of empirical observations is in his view that scientific ideas can never be proven true. An intriguing question is whether the assumption of incompleteness may change with systems biology, because genome-wide analysis “offers a waterproof counter to the concern that it is extremely difficult or impossible to know if black swans, i.e., qualitatively different mechanisms, are lurking elsewhere than in the islands of phenomena thus far chosen for causal analysis" (Davidson, Chapter 6).

A related question is whether systems biology methods break with the principle of Occam's razor, which states that the simpler of two explanations should be preferred (Kolodkin, Chapter 17; Voit, Chapter 23). Whereas Kolodkin and Westerhoff have argued that Occam's razor is ill-suited for research in systems biology (Kolodkin and Westerhoff 2011; Kolodkin, Chapter 17), Gross (Chapter 10) argues that all research practices – including the actual research practice in systems biology – rely on a variety of simplifying assumptions and idealizations. Moreover, other contributors highlight how too many details can hinder understanding in biological research, and that parameterizing and validating data-rich models is a difficult challenge (e.g., Hofmeyr, Chapter 11; Noble, Chapter 21). It is thus debated to what extent complex and data-intensive models and simulations will free us from the current problems arising from the need to simplify problem spaces to make analysis tractable. Whereas some attempts to upscale models may lead merely to a reproduction of biological complexity in uncomprehensive models, some useful multi-level models have already resulted from systems biological research. Examples are models of the virtual heart that combine tissue geometry, cellular physiology, gene expression and ion transport. These models provide excellent case studies for philosophical analysis of the challenges of model validation in practice (Carusi et al. 2012; Kolodkin et al. 2011; Noble, Chapter 21).

Systems biology thus provides new sources for philosophical analysis of representational strategies for organizing and analyzing biological information. Whereas philosophy of science traditionally has focused on scientific texts, the affordances and limitations of different forms of representation are now becoming rich sources for philosophical analysis of the cognitive role of visualizations in systems biology (Bechtel, Chapter 2; Fagan, Chapter 8; Jaeger, Chapter 13; Jones, Chapter 14). Representational strategies in systems biology go beyond sequential box and arrow diagrams and include highly complex network models and phase space diagrams. The use of and emphasis on specific representational strategies also poses challenges for interdisciplinary collaboration, as scientists with different training often have different views on what is a good model for a specific purpose (Carusi, Chapter 5; Nersessian, Chapter 20; Rowbottom 2011). Similarly, preferences for specific representational strategies may reflect different explanatory goals in the scientific practice (see below).

Explanations and design principles

Rather than appealing to laws, philosophers of biology have argued that functional biology provides *mechanistic explanations* citing how biological functions arise from the interaction and organization of the component parts (Bechtel 2011; Bechtel and Richardson 1993, Machamer et al. 2000). There is currently a lively philosophical debate as to whether systems biology explanations are mechanistic or not. Whereas much research in systems biology straightforwardly supports and produces mechanistic explanations (Boogerd et al. 2013; Richardson and Stephan 2007), other research endeavors seem harder to reconcile with the mechanistic focus on decomposable and localizable parts and operations. Some have therefore argued that the integration of aspects from systems theory, engineering and physics in systems biology explanations reveals a need for novel philosophical accounts of explanation (e.g., Braillard 2010; Brigandt 2013; Gross 2015; Mekios 2015; Isaad and Malaterre 2015).

Mathematical analysis of networks offers a powerful extension to mechanistic heuristics of functional and structural decomposition by offering insights into generalizable features of how mechanisms are organized (Bechtel 2015). One prominent example is the research on network motifs that directly informs experimental analysis of concrete regulatory circuits (Levy and Bechtel 2013). In this context, the intensified focus on generalizable organizational features and quantitative dynamic modeling results in updates and improvements of mechanistic accounts but not a departure from these. In response to developments in systems biology and other mathematically intensive research fields, some philosophers have therefore called for an updated and extended *dynamical mechanistic account* (Bechtel, Chapter 2;

Bechtel and Abrahamsen 2011; 2012; Brigandt 2013, see also Jaeger, Chapter 13; Mekios, Chapter 18). While systems biology seems to offer new ways of providing mechanistic explanations, other aspects of systems biology may be better described as non-mechanistic approaches (Gross, Chapter 10; see also Jones 2014; Chapter 14). For instance, some scholars have argued that some practices of modeling and explanation are better described through appeals to law-like explanatory ideals (Fagan, 2016; Chapter 8; Green, Fagan and Jaeger 2015), topological explanations (Huneman 2010; Jones 2014), or design explanations (Braillard 2010; Boogerd, Chapter 4; Wouters 2007). The diversity of explanatory ideals in systems biology creates new venues for scientific and philosophical analysis but also poses challenges for interdisciplinary collaboration (see section below).

Gross (Chapter 10) and Nersessian (Chapter 20) stress the importance and implications of the increasing reliance on methodologies and theoretical frameworks from physics and engineering. Many researchers in systems biology have a background in engineering, and functional language drawing on circuit analogies and concepts like noise, control, amplifiers, filters, robustness etc. is becoming more prominent. Whereas this language is compatible with functional language in biology in general, this "way of thinking" in systems biology is often accompanied by an increasing interest in identifying rather abstract organizational features that *in general* make a functional system able to exhibit specific capacities. The influence from control and systems theory on reasoning in systems biology suggests that it may be possible to reach an abstract, system-level understanding of basic functional schemes without a detailed understanding of specific mechanisms (Green 2015b; MacLeod and Nersessian 2015). Systems biology has brought about a new topic of philosophical research, namely the implications of *design principles* and *organizing principles* and their significance for biological understanding (Braillard 2010; Green and Wolkenhauer 2013; Mesarović, Chapter 18; Savageau 1976; Voit 2003; Wolkenhauer, Chapter 24). Among the relevant questions are not only whether these are compatible with mechanistic explanations or explanatory in their own right, but also whether philosophers of biology should pay more attention to other scientific aims than explanation. Alternative candidates include prediction, control and design (Brigandt et al. forthcoming; Kastenhofer 2013a; 2013b; MacLeod and Nersessian 2015;).

Another important question is how far we can get with an engineering perspective in biology. Although design principles and organizing principles are often used interchangeably, the preferences for one of these terms also reflect a concern with possible limitations of an engineering approach to biological systems. This question was already a theme in the early work of Bertalanffy and Mesarović (Drack, Chapter 7; Green and Wolkenhauer 2013), but it has regained its relevance in contemporary discussions about research methodologies in systems biology and about the fundamental question of what life is (Boogerd, Chapter 4; Braillard 2015; Boudry and Pigliucci 2013; Calcott et al. 2015; Nicholson 2013). Is there something fundamental and distinct about living systems? If so, can it be captured in a formal theoretical framework? How far can we go with engineering-approaches in biology? And what roles do functional and evolutionary features play in such a systems view of the organism?

Functional and evolutionary systems biology

The first book on philosophy of systems biology, edited by Boogerd, Bruggeman, Hofmeyr and Westerhoff (2007), emphasized the relative autonomy of functional biology from evolutionary biology. Except for the recent interest in modeling, experimental analysis and especially mechanistic explanations, much of philosophy of biology was until recently dominated by evolutionary biology. The intensified attention to functional biology with (philosophy of) systems biology is welcomed by many contributors in this volume (e.g. Boogerd, Chapter 4; Fagan, Chapter 8; Gross, Chapter 10; Hofmeyr, Chapter 11; Wolkenhauer, Chapter 24). Hofmeyr (2007) rephrased Dobzhansky's dictum that 'nothing in biology makes sense except in the light of evolution' in the context of systems biology to the following: 'nothing in an organism makes sense except in the light of a functional context'. Boogerd (Chapter 4) goes one step further in suggesting that 'many areas in systems biology make sense *without* the light of evolution'. The resistance to an all-encompassing evolutionary interpretation stems in part from a skepticism about the etiological theory of functions (i.e., function as selected effects). Accounts of whether and how a trait was selected often seem unnecessary for the functional analysis (Boogerd, Chapter 4). Systems biology thus opens for the possibility that design thinking, and design explanation, can be dissociated from evolutionary assumptions at least in some contexts (Green 2014; Green, Levy and Bechtel 2015; Wouters 2007).

In recent years, the new branch of *evolutionary systems biology* has emerged (Jaeger, Chapter 13; Soyer 2012, ed.). An important aim of evolutionary systems biology is to supplement evolutionary studies with a quantitative analysis that is also forward-looking in focusing on how the regulatory structure of biological networks influences the potential for evolutionary change. As Boogerd (Chapter 4) notes, evolutionary systems biology has provided yet another rephrase of Dobzhansky's dictum, namely that 'nothing in biology makes sense except when properly quantified in the light of evolution".[1] Experimental microbial evolution and *in silico* evolutionary simulations offer new possibilities for understanding the details of how particular regulatory processes have evolved. Systems biology may also bring about an understanding of the dynamic potential for change via a combination of experimental data and mathematical analysis drawing on dynamical systems theory (Jaeger and Cromback 2012; Jaeger and Monk 2014). Time will show whether systems biology will facilitate a new or extended "modern synthesis" of evolutionary biology (Boogerd, Chapter 4; O'Malley 2012). In addition to the synthesis of the theoretical framework of evolution by natural selection and Mendelian genetics in the beginning of the 20th Century, many scholars have argued that a modern theory of evolution should also be able to account for the development and evolution of biological form (Drack, Chapter 7). Important notions in such an extended synthesis are evolvability, robustness, adaptive and epigenetic landscapes, and phenotypic plasticity (Pigliucci 2007), and modeling and simulations tools from systems biology seem particularly suited for this purpose (Wagner 2012). A related question is whether philosophy of systems biology will be engaged with some of the new questions raised in the context of microbiology (Boogerd, Chapter 4; O'Malley 2013).

Systems biology may also bring together research fields that were previously divorced due to differences in epistemic standards. Aside from aiming to bridge between ideas from general systems theory and experimental approaches, structuralist theories of pattern formation may regain their relevance in systems biology (Green, Fagan and Jaeger 2015). According to structuralists, many patterns observed in nature are not only products of random genetic variation and natural selection, but result from more general constraints imposed by complexity (e.g., Goodwin, 1994). Structuralists have emphasized the need to not only explain how natural selection leads to preservation and adaptation of biological structures but also how patterns of variation - such as spatial orientation and morphological patterning in plants - arise in the first place. Many experimental biologists have regarded structuralism as a rather speculative approach to development and evolution. But since it is now possible to mathematically reverse engineer the dynamic structure of some gene regulatory networks from experimental data, systems biology may provide new insights to how form and function are related to specific regulatory structures and investigate evolutionary transitions *in silico* (see Jaeger, Chapter 13 and references therein). An exciting open question for the future of evolutionary systems biology is also whether the new experimental and computational approaches will turn evolutionary systems biology into a more predictive research field (Papp, Notebaart and Pall 2012), or whether it will lead to discoveries of further challenges of biological complexity.

[1] http://evolutionarysystemsbiology.org, accessed 28-07-2016.

Interdisciplinary Collaboration and Science Education

Interdisciplinary integration is the name of the game in systems biology (O'Malley and Soyer, 2012; Mekios, Chapter 18), but bridging between disciplinary differences is by no means an easy task. Several contributors highlight the difficult challenges for collaboration among researchers with different educational backgrounds (see e.g., Fagan, Chapter 8; Hohmann, Chapter 12; Kastenhofer 2007; Nersessian, Chapter 20; Voit, Chapter 23). From a philosophical perspective, such challenges can be important sources of insight into different epistemic ideals that are operative in science. The disciplinary gaps also afford a unique opportunity for philosophy to contribute positively to science and science education. Diagnosing the failures and problems in interactions between scientists can help facilitate scientific collaboration because differences can be clarified and discussed (e.g., Carusi, Chapter 5; Fagan, Chapter 8; Gross, Chapter 10; Jones, Chapter 14; Kastenhofer 2013a; Nersessian, Chapter 20, Voit, Chapter 23).

A common problem faced in the interdisciplinary practices of systems biology is the gap between the traditions of experimentalists and modelers. Nersessian's (Chapter 20) empirical studies of collaboration among modelers and experimentalists in integrative systems biology reveal interesting insights into how researchers often have "blind spots to the needs, values, or constraints of the other camp". For example, modelers ask for certain kinds of data that experimentalists do not think are worthwhile or even possible to produce. In turn, experimentalists may lack insight into the constraints and potentials of modeling, or may see the result of a model as simply reproducing the experimental finding *in silico*.[2] A very similar problem has been discussed in the context of stem cells research where prioritization of different standards of explanation has blocked collaboration and communication (Fagan 2016; Chapter 8). Modelers drawing on dynamical systems biology view *in silico* reproduction of dynamic behaviors of stem cells as a major breakthrough and picture their approach as superior to the mechanistic analysis conducted by experimentalists. Experimentalists have, however, largely ignored these contributions as they see these as merely restating what is already known about the system. In Fagan's view, the failure to communicate is at least partly due to the different standards of explanation held by the two groups, i.e. whether generalizable law-like principles or concrete mechanistic explanations are the end goal (see also Green, Fagan and Jaeger 2015).

Another aspect of the problem is the failure to understand in sufficient detail the methods that particular scientists are not trained in. This problem has important implication for science education in systems biology. Hohmann (Chapter 12) contends that students are often poorly prepared to enter a higher education program in systems biology because prior education typically is discipline-oriented, whereas systems biology is inherently interdisciplinary and requires the combination of different theoretical frameworks. Specifically, the lack of proper mathematical training in educational programs for experimental biologists makes it challenging for students to adopt a systems biology approach (see also Voit, Chapter 23). Equally important, modeling complex living systems is a challenging task without experimental or biological training (Nersessian, Chapter 20). As Nersessian points out, researchers involved in interdisciplinary collaborations need to develop interactional expertise (Collins and Evans 2002) that enables cross-disciplinary communication and conceptual understanding of other research practices.[3] Moreover, the studies of Nersessian's group have shown that successful interdisciplinary collaboration, in addition to interactional expertise, involves what she calls *epistemic awareness* of the differences in the often implicit assumptions and commitments about what constitutes good research.

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[2] As pointed out by Boogerd (personal communication), a high-quality model will indeed reproduce experimental findings, but can also be used to do so-called computer-experiments, i.e. experiments that are not yet done or that just cannot be done in reality. For instance, they may be used to test design explanations (Wouters 2007) or to model evolutionary trajectories (Jaeger, Chapter 13). The evidence status of this kind of model results is an interesting epistemological question on its own, and disagreement on this question among scientists can also be a source of insight to different epistemic cultures (Carusi, Chapter 5).

[3] Interactional expertise does not require expertise to make specific contributions to the other field.

One way to deal with the problem is to establish and improve research infrastructures. Hohmann (Chapter 12) points to the fruitfulness of current efforts in Europe such as matching expertise to facilitate the collaboration between experimentalists and modelers. Another strategy is making modeling tools and tutorials available online for experimentalists to gain a better understanding of modeling procedures. Nersessian (Chapter 20) and Voit (Chapter 23) make concrete recommendations for how philosophers, cognitive scientists and psychologists could contribute to the development of educational programs for "cognitively flexible" future systems biologists. One example of such an initiative was an introductory problem-solving systems biology class for graduate students designed to scaffold cognitive processes required for investigating a specific but complex problem in biomedicine (Voit 2014; Voit, Newstetter and Kemp 2012). Another option is to set up an exchange program so that graduate students can spend sufficient time in the other "camp" to get an impression of the methods, values and challenges in the other field. Nersessian (Chapter 20) reports that two of their graduate student modelers spent two months learning experimental procedures, collecting data and interacting with biologists. This gave them a better understanding of the practical constraints on experimental practices and of the questions important to experimentalists. Similarly, as indicated above, experimentalists could improve their understanding of the implications and affordances of different modeling techniques if they took a basic course in mathematical and computational modeling (see also Voit 2012). Importantly, neither of the contributors seems to support the idea that systems biology education should become interdisciplinary from the start. The tradeoff between transdisciplinary scope and specialized expertise is an important topic of interest to both science education and philosophy. Addressing it may require preserving some disciplinary boundaries despite the increasing emphasis on interdisciplinarity in modern science (Andersen 2013, 2016).

Research modes and institutional structure

Research in systems biology requires new educational skills but also leads to reflections on the institutional frames for modern science (Davidson, Chapter 6; Jaeger, Chapter 13; Kastenhofer, Chapter 15; Wolkenhauer, Chapter 24). Several contributors highlight that the embedding of systems biology in technologically mediated funding and rewards systems raises important challenges for scientific innovation.

While researchers increasingly acknowledge the depths and scope of biological complexity, they continuously face constraints in terms of funding opportunities, available methods and time-frames allowed for conducting research projects. Wolkenhauer (Chapter 24) observes with regret what he describes as a scientific culture of optimism and unreasonable expectations. Grant proposals and press releases continuously give the impression that technological innovations finally have positioned us to achieve long-awaited breakthroughs in biology and medicine, even though the methodologies pursued are highly limited and fail to do justice to the biological complexity. Jaeger (Chapter 13) also expresses his frustration with what he sees as a noxious trend in modern science and society to focus on immediate and quantifiable payoffs. When operating under a pressure for immediate results, research projects may aim for low hanging fruit that does not solve the deeper conceptual or societal problems (see also Drack, Chapter 7; Lazebnik 2010; Wolkenhauer and Green 2013). Given the complexity of living systems, ignoring the profound uncertainties and difficulties associated with research methodologies can hinder progress in dealing with more fundamental problems that require time for contemplation and creativity.

Similar points are made by Gross (Chapter 10) who highlights the unfortunate implications of oversimplified and overambitious rhetorical statements. Although it may be obvious to the scientific community that such statements are overoptimistic, they may influence the way in which scientific research is organized and resources are allocated (see also Green and Vogt 2016). Whereas these issues are broad topics concerning the culture of science in general, they may be particularly relevant in connection with systems biology because there is a development towards "big science" projects involving multiple international institutions and funding bodies investing heavily in applied science (Davidson, Chapter 6; Jaeger, Chapter 13). Systems biology provides unique opportunities for developing radically different methodologies but also runs a risk of wasting resources on projects leading nowhere. Gross (Chapter 10) suggests that philosophers, as more neutral observers, may be able to provide a useful "birds-eye" perspective on the affordances and limitations of different approaches, and on the general development of the field (see also Wolkenhauer, Chapter 24; Voit 2016).

A related issue is the ramification of data-intensive strategies that have been argued to fundamentally change the way that science is done (cf. Allen 2001, Anderson 2008, Kell and Oliver 2003). On one hand, the massive data-production and increase in computational power raise hopes that more comprehensive models and datasets can better exclude alternative explanations for a given phenomenon (Davidson, Chapter 6). On the other hand, the enthusiasm about data-intensive biology has solicited concerns about what Hofmeyr (Chapter 11) calls the "omics delusion" – the idea that understanding will emerge from measuring everything we possibly can inside a cell under different conditions. Davidson (Chapter 6), Drack (Chapter 7) and Peter (Chapter 22) also criticize the idea that "data can speak for themselves." Similarly, philosophers have taken issue with the idea that correlation-based analysis should be a more bias-free research approach (Gross, Chapter 10; Krohs 2012). This is not a criticism of data-intensive research as such but of a practice that draws grand conclusions from low-quality data, and that claims to be bias-free while relying on significant assumptions about modular decomposability of biological networks. Whereas data-intensive strategies may create new interesting research opportunities, it is important to discuss whether new strategies are more efficient, and the extent to which these need to be better integrated with experimental analysis (Davidson, Chapter 6; Gross, Chapter 10; Hohmann, Chapter 12; Noble, Chapter 21).

These issues are also connected to questions about how data sources are produced, curated and used in practice (Leonelli 2012; 2014). Procedures for standardization are important - but so is the evaluation of what kinds of biological data are relevant for addressing specific questions. Although the life sciences currently experience what has been metaphorically described as a flood of data or a data deluge, the lacking availability of high quality time course data continues to be one of the limiting factors for systems biology research (Wolkenhauer, Chapter 24). Similarly, although we today have tremendously complex network models developed from high-throughput data, Jaeger (Chapter 13) argues that we need to go beyond static "hairball" networks that fail to capture how biological processes operate and change over time.

Systems biology as the future of medicine?

Systems biology is expected to play a central part in future medicine, and projects under the labels of systems medicine, personalized medicine, P4 medicine and precision medicine indicate the directions we can expect medicine to follow (Hood and Flores 2012; Loscalzo and Barabasi 2011; Voit and Brigham 2008; Wolkenhauer et al. 2013). At the same time, it is still unclear what it means to personalize medicine and whether the visions for the future are realistic (De Grandis and Halgunset 2016; Green and Vogt 2016; Vogt et al. 2014). Multi-scale simulations will likely become an ever increasing topic of philosophical interest because of their deep epistemic and social implications. Multi-scale cardiac models with practical implications for treatment and drug choice are already being developed, and steps are currently taken to develop a *Virtual Physiological Human* or *digital patient models* (Kohl and Noble 2009; Kolodkin et al. 2011; Kolodkin, Chapter 17). As Carusi (Chapter 5) highlights, multi-scale simulations may have the potential of replacing some experimental *in vivo* and *in vitro* studies with great implications for biomedical research, clinical trials and also animal welfare. Moreover, large-scale simulations developed in systems biology bring new light to philosophical discussions about the relation between experiments and simulations. What are the differences and similarities between experiments and simulations? Can experiments alone be said to provide novel evidence in biological research, or also computational models? Philosophical analysis of the development and use of complex multi-scale models show that the relation between experiments and simulations are much more complex and intertwined than often assumed (Carusi et al. 2012; see also note 2).

The integration of systems biology with biomedical research and health practices also means that philosophy of systems biology is likely to become more concerned with social and ethical issues. Carusi (Chapter 5) highlights that the issues will involve not only the well-known ones of data security, anonymity, confidentiality, and consent, but also ones about the changing ethos and values of science as the idea of precision medicine is embedded in a community ethos for producing, sharing and standardizing data. The large-scale organization of biomedical efforts raises important questions about ownership and authorship of data (Ankeny and Leonelli 2015), about what it means to be a life scientist in these contexts, but also about what role citizens will play in data production in the future. Some proponents of systems medicine have highlighted the need for new social constellations where patients and citizens will take a more active role in research as providers of health data (Hood and Flores 2012). With more encompassing datasets (e.g., from genomics and self-monitoring) and powerful systems biology models, the hope is that future medicine will be able to predict and prevent a number of diseases that today require expensive and often inefficient treatments.

The intensified focus on disease prediction in systems medicine raises exciting possibilities for the future but also concerns about the clinical validity and utility of the new models, about patient responsibility and about social values (Green and Vogt 2016). Carusi (Chapter 5) stresses how biological sciences play a crucial role in shaping and legitimating ideologies concerning humans, animals, environment, and the relations between them. While systems biology can be described as emancipating in moving away from the kind of reductionism pursued in molecular biology (Kastenhofer, Chapter 15), the optimism for prediction and control in some streams of systems medicine is based on a simplistic picture of human society and deterministic ideals (Carusi, Chapter 5). While a holistic approach may liberate biomedical research from one kind of reductionism (focused on individual components), the replacement may be a *technoscientific holism* that results in an increasing medicalization of healthy people through increasing monitoring of biomarkers (Vogt et al. 2016). Thus, systems medicine has the potential to also change our view on health and disease – for better or worse. Such issues display a fertile ground for philosophy of systems biology to take a more active part in shaping the developing approaches of systems biology and systems medicine. Ultimately, the development of systems medicine provides a unique opportunity for collaborative projects involving systems biologists, other natural scientists, clinicians, historians of science, social scientists and philosophers.

3. Future perspectives for philosophy of systems biology

Systems biology has received special attention from philosophers because philosophical questions have been central to systems biology from the outset. As an inherently interdisciplinary approach, systems biology continuously reevaluates the methodological and ontological assumptions of the life sciences (see Boogerd et al. 2007; Gross, Chapter 10; Kastenhofer, Chapter 15). Philosophers are often explicitly invited to take part in this discourse (e.g., Boogerd, Chapter 4; Voit, Chapter 23; Wolkenhauer, Chapter 24). Insofar as philosophy is concerned with reflections on how we understand the world and the implications of specific assumptions or world views, the connection between philosophy and science is not surprising. Many contributors of this volume emphasize that there is no sharp divide between philosophy and scientific inquiry, and that all science is based on some philosophical assumptions (e.g., Fagan, Chapter 8; Hofmeyr, Chapter 11; Noble, Chapter 21; Wolkenhauer, Chapter 24). Philosophy of science was, however, for many years divorced from scientific practice and concerned mainly with abstract logical and conceptual analysis of scientific theories as propositional argument structures. As a result, many philosophers genuinely interested in scientific practice have experienced some resistance from practicing scientists who question whether philosophical analysis has anything to offer to science. Against this background, many philosophers have been positively surprised by how many systems biologists are open to interactions. The number of joint publications by philosophers and practicing scientists is a positive indication of the mutual interest in philosophy of systems biology (e.g., Boogerd et al. 2013; Calcott et al. 2015; Carusi et al. 2012; Drack and Wolkenhauer 2011; Green, Fagan and Jaeger 2015; O'Malley and Soyer 2012; Jones and Wolkenhauer 2012).

Although philosophers and practicing scientists are often interested in the same questions, philosophers typically approach these from a greater distance (Fagan, Chapter 8). In the space between an unavoidably interested and specialized perspective of practicing scientists and the reflective distance of philosophy lies a unique potential for critical reflection that is informed by how science is actually done (see also Nersessian, Chapter 20). Philosophers can gain understanding of the experimental and mathematical procedures involved in systems biology research, but scientists may also benefit from the identification of assumptions, implications and value-laden aspects of the scientific practice that are often only visible from a greater distance.

Wolkenhauer (Chapter 24) expresses the utility of philosophy as a way to avoid getting swamped by scientific detail that may take focus away from the important questions. At the same time, he calls for a more active participation of philosophers in current research. Similarly, Jones (Chapter 13) argues that while philosophers are often on the sidelines of systems biological activities, they are equipped for an advisory or assistant role too. However, as pointed out by Carusi (Chapter 5) and Nersessian (Chapter 20), to perform such a role professional academic philosophy must reinvent itself and become more informed by and engaged with scientific practice. Nersessian highlights the great potential of empirical methods such as interviews and observations studies to inform philosophical analysis. Carusi stresses that collaboration across philosophy and science requires a willingness to set aside purely philosophical concerns and motivations for the sake of being open to what is important to scientific practice. A common experience for philosophers is that technical terms may be used in different and often more indeterminate ways in science compared to philosophical discussions. Although philosophy can assist science in conceptual clarification of the meaning of important terms such as model, validation, mechanism etc. in different fields, it is far from clear that scientific practice requires that the terms are pinned down to analytical definitions (Carusi, Chapter 5). Thus, collaborations across science and philosophy must also navigate in adaptive problem spaces (Nersessian, Chapter 20) that require epistemic awareness of the different aims, conceptions and methods in philosophy and scientific practice.

We are only now beginning to discuss, let alone understand, what the research strategies and theoretical frameworks in systems biology imply for our prospects of solving great puzzles provided by biological complexity. Systems biology will generate food for philosophical thought for many years to come. Moreover, the expectation that systems biology will have great impact on biomedical research makes this approach a topic relevant to anyone interested in understanding the implications of scientific developments for science and society.

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